



## Review

Engineering vaccines and niches for immune modulation<sup>☆</sup>Alberto Purwada<sup>a</sup>, Krishnendu Roy<sup>b</sup>, Ankur Singh<sup>c,\*</sup><sup>a</sup> Department of Biomedical Engineering, Cornell University, Ithaca, NY 14853, USA<sup>b</sup> Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA<sup>c</sup> Sibley School of Mechanical and Aerospace Engineering, Cornell University, Ithaca, NY 14853, USA

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## ABSTRACT

Controlled modulation of immune response, especially the balance between immunostimulatory and immunosuppressive responses, is critical for a variety of clinical applications, including immunotherapies against cancer and infectious diseases, treatment of autoimmune disorders, transplant surgeries, regenerative medicine, prosthetic implants, etc. Our ability to precisely modify both innate and adaptive immune responses could provide new therapeutic directions in a variety of diseases. In the context of vaccines and immunotherapies, the interplay between antigen-presenting cells (e.g. dendritic cells and macrophages), B cells, T helper and killer subtypes, and regulatory T- and B-cell responses is critical for generating effective immunity against cancer, infectious diseases and autoimmune diseases. In recent years, immunoengineering has emerged as a new field that uses quantitative engineering tools to understand molecular-, cellular- and system-level interactions of the immune system and to develop design-driven approaches to control and modulate immune responses. Biomaterials are an integral part of this engineering toolbox and can exploit the intrinsic biological and mechanical cues of the immune system to directly modulate and train immune cells and direct their response to a particular phenotype. A large body of literature exists on strategies to evade or suppress the immune response in implants, transplantation and regenerative medicine. This review specifically focuses on the use of biomaterials for immunostimulation and controlled modulation, especially in the context of vaccines and immunotherapies against cancer, infectious diseases and autoimmune disorders. Bioengineering smart systems that can simultaneously deliver multiple bioactive agents in a controlled manner or can work as a niche for in situ priming and modulation of the immune system could significantly enhance the efficacy of next-generation immunotherapeutics. In this review, we describe our perspective on the important design aspects for the development of biomaterials that can actively modulate immune responses by stimulating receptor complexes and cells, and delivering multiple immunomodulatory biomolecules.

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## 1. Introduction

For many years, the field of biomaterials has involved immunology-related considerations in the context of immune reactions to implanted synthetic/natural materials. However, over the past decade the focus of many bioengineers and clinicians has been shifting towards immunoengineering approaches that include, but are not limited to, biomaterials-based vaccines and immunotherapies, cell and gene therapy for immunomodulation, and engineered immune system microenvironments. These research areas embrace a comprehensive list of fundamental and translational immunology-associated problems in a wide array of diseases including chronic

and acute infections, autoimmune diseases, aggressive cancers, allergies, etc.

Biomaterials-based immunoengineering is a nascent field that lies at the interface between materials science and immunology, and works by exploiting unique characteristics of host–material interactions, cellular signaling within the host, spatiotemporal delivery and localization of antigen/adjuvants, and transport of biological fluids. It is clearly challenging to engineer biomaterials that influence immune cells in a highly controllable manner, since this requires a complex design process with a detailed understanding of both the physiochemical properties of biomaterials and the fundamental biology of the immune system. Nevertheless, with recent failures of traditional immunotherapy approaches to treat existing disease due to immune evasion, rapid systemic clearance, tedious manufacturing processes and the large doses of therapeutics used (which increases both the overall cost of treatment and the risk of systemic cytotoxicity), the importance of this approach is starting to be recognized.

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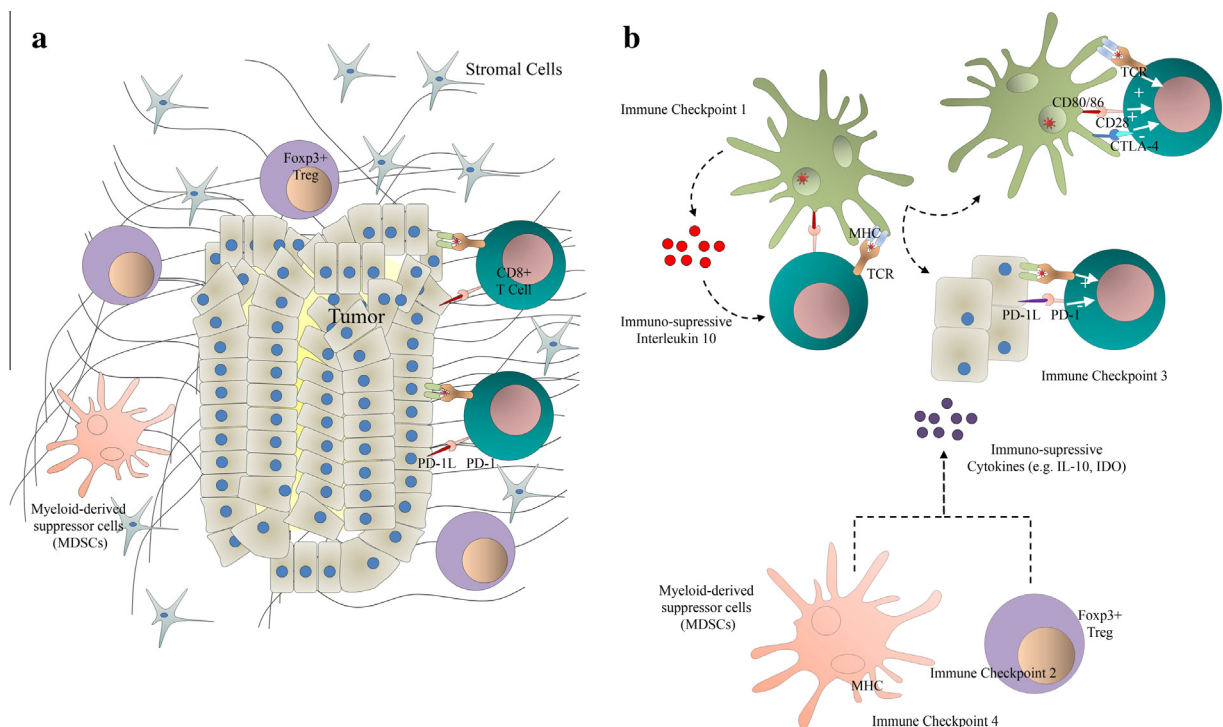
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The challenges to traditional immunotherapy can be further illustrated in the case of tumors and pathogens that cause chronic infections while evading or manipulating our immune system [1–3]. In contrast to acute infections where the infected cells induce a rapid humoral and cellular immunity with massive expansion of antigen-specific clonal B and T cells in germinal centers and lymph nodes followed by fast clearance of infected cells (in a few days–2 weeks), chronic infections and tumors persist for significantly longer times (months to years) due to immune evasion or inefficient priming of immune cells. Specifically, tumors can exploit the immune-regulatory networks that prevent recognition of self-antigens on host cells from immune cells. Ideally a tumor-specific immune response is tightly regulated by the level of expression of tumor antigens and their recognition by dendritic cells (DCs). Many tumors, such as lymphomas, sarcomas and carcinomas, express tumor-specific antigens, however these are poorly immunogenic self-antigens [4–7] and DCs often fail to recognize them simply because central tolerance to self-antigens is the first defensive step against self-destruction through autoimmunity. Although the poor antigenicity might be thought to be the primary cause of immune evasion, recent studies have indicated the presence of antigenic tumor cells in mice and humans with abnormally overexpressed healthy or somatically mutated genes [8–11]. Recent studies further indicate that cancer immunosuppression is closely tied to development of an immunosuppressive microenvironment [12,13]. Such microenvironments (Fig. 1a) extend from the tumor development site to secondary lymphoid organs, and sometimes lymphoid organs themselves are the primary site of infection such as in lymphomas that may develop in the lymph nodes and spleen. Tumor microenvironments are rich in immunosuppressive cytokines such as interleukin (IL)-10 and transforming

growth factor- $\beta$  (TGF- $\beta$ ). Elegant studies with subcutaneously injected sarcomas suggest that the tumor site is an immune-privileged site with an absence of primed cytotoxic T-cell response, and that tumor growth is strictly correlated with the failure of tumor cells to transport into the draining lymph nodes [14]. Within the tumor microenvironment, the resident stromal cells compete with DCs for tumor antigens and the stroma-induced increase in interstitial fluid pressure inside the tumor prevents T cells from reaching the diseased cells [15,16]. Cytotoxic T cell inhibition is further synergized by an increase in regulatory T cell (Treg) numbers in the tumor environment and by receptor–ligand interactions between specific molecules expressed by the tumor cells and T cells. The CD28/cytotoxic T-lymphocyte antigen-4 (CTLA-4):B7-1/B7-2 receptor–ligand interaction represents the classic example of an immune inhibitory pathway. Another critical pathway is the PD-1 (programmed death 1) inhibitory pathway that can modulate the T-cell response against self-antigens, virus-infected animals [17,18] and has demonstrated promising clinical outcomes in cancer [19,20]. Blocking the CTLA-4, PD1 and similar suppressive checkpoints (Fig. 1b) could provide a new regime in cancer immunotherapy and has been discussed elsewhere [21–23].

Similar to the immunosuppressive environment created by tumor cells, the ability to acquire protective immunity against infections such as malaria is compromised by *Plasmodium* parasites which actively interfere with the development of adequate memory T-cell responses [24] such that the resulting partial immunity predisposes the patient to a risk of reinfection. While subunit vaccines eliciting predominantly T-helper type 1 (Th1) immunity are essential for cancer and most infections, fighting against malaria requires a more balanced Th1/Th2 response from antigen-specific T cells [25]. The role of Th1 and Th2 cells and the central role of



**Fig. 1.** Immunosuppressive tumor Microenvironment. (a) Tumors consist of a wide array of immune and stromal cells along with malignancy supporting extracellular matrix and cytokines secreted by infiltrating cells such as MDSCs, DCs, neutrophils, natural killer cells and lymphocytes. (b) Immune checkpoints 1–4 regulate key components involved in generation of immune response. The cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)-mediated immune checkpoint is induced in T cells when antigen is first presented by DCs to the T cells. The programmed cell death protein 1 (PD1) pathway-mediated immune checkpoint is induced when activated T cells with high expression levels of PD1 encounter PD1 ligands on tumor tissues, which suppress the T-cell response. PD1 ligands are upregulated in tumor tissues in response to interferon- $\gamma$  produced by activated T cells. Cytokines such as IL-10 and indoleamine-2,3-dioxygenase (IDO) produced by DCs, Tregs and other cells function as immunosuppressive checkpoints against cancer.

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